[disease] comprising administering to said mammal a safe and effective [androgen responsive or mediated disease] amount of the formulation of Claim 10.

Claim 12. (Amended) [A] The pharmaceutical formulation of claim 10 further comprising [containing; a safe and effective amount of a compound defined by claim 1;] an alpha 1 adrenergic receptor blocker[; and a pharmaceutically acceptable carrier thereof].

Claim 15. (Amended) A method of treating an androgen responsive or mediated condition [disease] in a mammal suffering from said condition [disease] comprising administering to said mammal a safe and effective [androgen responsive or mediated disease] amount of the formulation of Claim 12.

Claim 16. (Amended) [A] The pharmaceutical formulation of claim 10 further comprising [containing; a safe and effective amount of a compound defined by claim 1;] an anti-estrogen selected from the group consisting of: clomiphene and tamoxifen[; and a pharmaceutically acceptable carrier thereof].

Claim 18. (Amended) A method of treating an androgen responsive or mediated condition [disease] in a mammal suffering from said condition [disease] comprising administering to said mammal a safe and effective [androgen responsive or mediated disease] amount of the formulation of Claim 16.

Claim 19. (Amended) [A] The pharmaceutical formulation of claim 10 further comprising [containing; a safe and effective amount of a compound defined by claim 1;] an anti-androgen[; and a pharmaceutically acceptable carrier thereof].

Claim 21. (Amended) A method of treating an androgen responsive or mediated condition [disease] in a mammal suffering from said condition [disease] comprising administering to said mammal a safe and effective [androgen responsive or mediated disease] amount of the formulation of Claim 19.

Claim 22, in formula (VII), delete "CO_2X" and substitute therefor --COX--.

REMARKS

The above amendments to page 1 of the specification are made to clarify Applicants' claim to the benefit of USSN 08/123,280. Applicants appreciate the Examiner drawing our attention to this matter. The above amendment to Claim 22 is made to correct typographical errors. The above

amendments to Claims 3, 8, 9, 11, 15, 18, and 21 are made to change "disease" to "condition" and to correct typographical errors.

Claims 12, 16, and 19 have been amended to change dependency in order to more clearly show relationships and groupings between claims.

Applicants believe that copies of all the documents cited in the Information Disclosure Statements were previously supplied to the Examiner. If any copies are missing please let us know and we will be happy to supply another copy.

The Examiner requests a new title because the current title is allegedly "not descriptive." Applicants do not understand why the Examiner believes the current title is not descriptive. The present claims are directed to certain androstenone derivatives, uses therefor, methods of preparation thereof, etc. Applicants believe the title is descriptive. Applicants request that this objection be withdrawn. However, Applicants would be happy to consider any title suggestions from the Examiner.

The Examiner has required a restriction between Invention I (Claims 1-4, 6, and 10), Invention II (Claims 5-7), Invention III (Claims 8, 9, and 11), Invention IV (Claims 12-14, 16, 17, 19, and 20), Invention V (Claims 15, 18, and 21), Invention VI (Claims 22-24). Applicants elect with traverse Invention I (Claims 1-4, 6, and 10). Applicants are confused by several aspects of the grouping of claims. Applicants have discovered novel compounds with surprising properties. Applicants have claimed compositions containing these compounds, methods for making the compounds, and methods for using these compounds. If a restriction is made there should be at most four groups: (1) claims directed to compounds and simple composition, (2) claims drawn to processes for making the compounds of group 1, (3) claims drawn to methods of using the compounds and compositions of group 1, and (4) intermediates.

The Examiner's Invention I is said to be "drawn to compounds and simple composition," yet Invention I includes Claims 4 and 6 which are drawn to methods for making the compounds. Therefore, Claims 4 and 6 do not appear to belong to Invention I. In addition, Claims 12-14, 16, 17, 19, and 20 (Invention IV) are all drawn to simple compositions containing the compounds and appear to belong to Invention I as characterized by the Examiner. Applicants note that if Claim 1 is patentable then Claims 12-14, 16, 17, 19, and 20 must be patentable. In Summary, Invention I, drawn to compounds and simple composition, should be Claims 1-3, 10, 12-14, 16, 17, 19, and 20.

The Examiner's Invention II is said to be for Claims "5-7, drawn to multiple processes for I." Note that as discussed above, Claim 6 was previously stated by the Examiner to be in Invention I. Also note that Claim 4, previously stated by the Examiner to be in Invention I, is also directed to a process for making the compounds of Invention I. In summary, Invention II, drawn to methods for making the compounds of Invention I, should be Claims 4-7.

The Examiner's Invention III (Claims 8, 9, and 11) is directed to "multiple methods of using" the compounds and compositions of Invention I. Claims 15, 18, and 21 (Invention V) are also directed to multiple methods of using the compounds and compositions of Invention I and should be included in Invention III. In summary, Invention III should be Claims 8, 9, 11, 15, 18, and 21.

The Examiner's Invention VI is correctly drawn to intermediates.

Applicants propose a maximum of four groups of claims: Group I (Claims 1-3, 10, 12-14, 16, 17, 19, and 20), drawn to compounds and compositions; Group II (Claims 4-7), drawn to methods for making the compounds of Group I; Group III (Claims 8, 9, 11, 15, 18, and 21), directed to multiple methods of using the compounds and compositions of Group I; and Group IV (Claims 22-24), drawn to intermediates.

If the Examiner agrees to the proposed modified grouping, Applicants elect Group I (Claims 1-3, 10, 12-14, 16, 17, 19, and 20) with traverse. Groups I and III should be Examined together. As stated in the MPEP § 803, "there are two criteria for a proper requirement for restriction . . . (2) there must be a serious burden on the examiner if restriction is not required." There is no such burden here. The same issues of teaching how to use and obviousness are present in both groups. Applicants note that many of the Examiner's § 112 and § 103 arguments in the rejections have been equally applied to claims from both Group I and Group III. If the Examiner prefers, Group III could be provisionally rejected as dependent on a rejected base claim (i.e. Claim 1). In summary, we propose examination of Claims 1-3 and 8-21 together. Please let us know if you agree to our proposal. Applicants do not traverse the restriction of non-elected Claims 4-7 and 22-24.

The Examiner has rejected Claims 1-24 "under 35 U.S.C. § 112, first and second paragraphs." This rejection is respectfully traversed. The Examiner details the rejection in 17 separate points. The two key themes of the rejection appear to be first that Applicants have not supported a reasonable showing of usefulness and second that Applicants have not

provided enough guidance on how to use the invention. These two key arguments will be addressed before addressing each point individually.

The Examiner's § 112, first paragraph, rejection for lack of usefulness must adhere to the recent PTO guidelines. On July 14, 1995, the PTO published its final Utility Examination guidelines for utility rejections based on 35 U.S.C. § 101 or § 112, first paragraph. In general, the guidelines state that an assertion of utility that would be considered credible by a person of ordinary skill in the art shall not be rejected based on lack of utility. The PTO's legal analysis states that "A § 112, first paragraph, rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under § 101 under these guidelines." Applicants have made a credible assertion of utility. The prior art, including art cited by the Examiner, shows a strong correlation between in vitro enzyme inhibition, rat in vivo, and human clinical data. See, for example, the references cited in the present specification on page 11, lines 14-19. Applicants note that Rasmusson discloses that acne vulgaris, seborrhea, female hirsutism, male pattern baldness, and benign prostatic hypertrophy are androgen mediated physiological conditions and that inhibitors of testosterone-5-alpha-reductase will serve to prevent or lessen such symptoms. See Rasmusson, Col. 1, Lines 17-63. Applicants also note that Rasmusson uses the word "condition" rather than "disease" in the claims. Applicants are willing to also use the word "condition" rather than "disease" in the claims. One of ordinary skill in the art would expect that compounds that inhibit androgens will be useful in the treatment of androgen mediated diseases or conditions. Based upon Applicants' demonstration that the claimed compounds inhibit the enzyme, it is credible that the compounds will be useful to treat androgen mediated diseases. Therefore, applicants request that this lack of usefulness rejection be withdrawn.

Second, the Examiner's § 112, first paragraph, rejection for lack of enablement must show that undue experimentation is required to practice the invention. One of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. As stated in MPEP § 2164, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." Optimization of dosing, and methods of administering drugs are well know to those of ordinary skill in the art. Human clinical trials will need to be run but these trials are standard operating procedure and are not a prerequisite for patentability. See, for example, Applicants' specification, pages 11-14, for a description of formulations and dosing. The art cited by the Examiner makes

similar claims with similar disclosure. Applicants note that Claim 2 in Rasmusson claims a method of treating the hyperandrogenic condition of acne vulgaris, etc., comprising administration of an effective amount of the compound of Rasmusson's Claim 1. Applicants see no reason why Applicants' similar claims do not also meet the requirements of 112.

In point 1 the Examiner asks whether the formula in Claim 22 is correctly shown. The Examiner is correct that the formula should be COX. Applicants regret any confusion caused by this error. The above amendments to Claim 22 and page 7 correct this error.

In point 2 the Examiner asks for the meaning of "androgen responsive or mediated disease." This term is clear to one of ordinary skill in the art and is explained in the specification. See, for example, page 1, lines 25-32. See also the references cited by the Examiner, for example, Rasmusson. An androgen mediated disease is a disease that is brought about by the action of androgens. Because this term is clear, Applicants request that this rejection be withdrawn.

In point 3, the Examiner asserts that baldness and hirsutism are not diseases. This is not correct. A disease is generally defined as "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown." See, e.g., Dorland's Medical Dictionary, W.B. Saunders company. The use of the word "disease" in the claims is clear and causes no confusion. However, Applicants would be willing to use the term "condition" instead of, or in addition to, "disease."

Points 4, 6, 9, and 14 all assert lack of usefulness which has been fully addressed above.

Points 5, 8, 10, 11 and 13 all assert lack of enablement based on insufficient teaching regarding how to use and has been fully addressed above.

Applicants believe that the above amendments to Claims 8, 11, 15, 18, and 21 correct the confusion pointed out in point 7. Applicants regret any confusion caused by this error.

In point 12 the Examiner asserts that there is no teaching how to make and use the compounds of Claims 22 and 23. This is not correct. The specification teaches how to make and use these compounds. See, for example, page 7, lines 9-19, and page 8, lines 1-18.

In point 15 the Examiner asks for clarification regarding the terms "alpha 1 adrenergic receptor blocker," "anti-estrogen," and "anti-androgen."

Because these terms are all well known to one of ordinary skill in the art, Applicants request that this rejection be withdrawn.

In point 16, the Examiner asks for clarification of the term "solvates." This term is well understood by those in the art and is explained in the specification, for example on page 4, lines 32-36.

The Examiner has rejected Claim 25 "under 35 U.S.C. § 102(e) as being clearly anticipated by Biollaz." This rejection is respectfully traversed. This rejection is improper because there is no Claim 25 in this case. Therefore Applicants request that this rejection be withdrawn.

The Examiner has rejected Claims 22 and 23 "under 35 U.S.C. § 102(e) as being clearly anticipated by Biollaz." This rejection is respectfully traversed. This rejection is improper because no reasons are given for the rejection. Therefore Applicants request that this rejection be withdrawn.

The Examiner has rejected Claim 3 "as the obvious method for making a mixture." This rejection is respectfully traversed. Claim 3 is not a "method for making a mixture." This rejection should be withdrawn because it is so unclear that Applicants cannot respond. Therefore, this rejection is improper and Applicants request that it be withdrawn

The Examiner has rejected Claims 4-6 "under 35 U.S.C. § 103 as being unpatentable over Kojima EP '094." This rejection is respectfully traversed. The Examiner's rejection is improper because of its reliance on Durden. In complete contrast to the Examiner's assertion that Durden stands for the proposition that the "use of analog in known conventional processes is not ordinarily patentable," Durden stated that such uses are "not necessarily" patentable. Durden, 763 F.2d 1406, 1408 (Fed. Cir. 1985). The Federal Circuit in Durden and in several cases after Durden stressed that there can be no general rule, that each case must be decided on its facts. See MPEP § 706.02(j) for a summary of the proper contents of a § 103 rejection. This rejection is improper because the Examiner has failed to state why the rejected claims are obvious. Applicants request that this rejection be withdrawn.

The Examiner has rejected Claims 4-6 "under 35 U.S.C. § 103 as being unpatentable over Rasmusson '071." This rejection is respectfully traversed. The Examiner's rejection is improper because of its reliance on Durden. See MPEP § 706.02(j) for a summary of the proper contents of a § 103 rejection. This rejection is improper because the Examiner has failed to state why the rejected claims are obvious. Applicants request that this rejection be withdrawn.

The Examiner has rejected Claims 1-3, and 7-11 "under 35 U.S.C. § 103 as being unpatentable over Rasmusson '071." The Examiner has rejected Claims 1-3, 7-11, and 18-21 "under 35 U.S.C. § 103 as being unpatentable over Gormley WO 233." The Examiner has rejected Claims 1-3, and 7-15 "under 35 U.S.C. § 103 as being unpatentable over Gormley WO 233." These rejections are respectfully traversed. These rejections share the same basic argument and will be addressed together. The Examiner is asserting that because structurally similar compounds are known to be alpha reductase inhibitors, it would be obvious to substitute Applicants' trifuloromethyl substituents for the generically disclosed methyl or halogen substituents. As stated in the MPEP § 706.02(j), "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference." The Examiner has failed to raise even a prima facie case for obviousness because the Examiner has pointed to no motivation in the art to make the Examiner's suggested modification. Therefore, Applicants request that these obviousness rejections be withdrawn.

Furthermore, even if a prima facie case were to be established, the unexpected potency and surprisingly long half-life of Applicants' compound renders the compound unobvious. See, for example, the present application, page 11, lines 9-14, and page 10, Table 1. As stated in the MPEP § 2144.09, "a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties." Therefore, Applicants request that these obviousness rejections be withdrawn.

The Examiner has rejected Claims 22-24 "under 35 U.S.C. § 103 as being unpatentable over Rasmusson '071." This rejection is respectfully traversed. The Examiner is not correct that the X in Rasmusson suggests halogen. Rasmusson defines X, and that definition does not include or suggest halogen. Because the Examiner in not correct that Rasmusson suggests halide, the Examiner has failed to establish a prima facie case of obviousness. Applicants request that this rejection be withdrawn.

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration of the rejections is requested. Please feel free to call me if you have an questions or to set up an interview.

Respectfully submitted,

Robert H. Brink

Robert H. Brink
Attorney for Applicants
Registration No.: 36,094

Date: Feb 22, 1996

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, North Carolina 27709
(919) 483-~~7506~~ 3323

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, DC 20231 on 2/22/96 in accordance with the provisions of 37 CFR 1.8.

Elaine Martens
Elaine Martens